IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Atty. Docket No: 5051-451IP

In re patent application of

Yuehua LI *et al.*

Group Art Unit: 1635

Serial No. 09/914,020

Examiner: Janet L. Epps-Ford

Filed: December 31, 2001

For: METHODS AND COMPOSITIONS FOR ALTERING MUCUS SECRETION

DECLARATION UNDER 37 C.F.R. §1.132

I, Indu Parikh, declare that:

1. I hold the position of President and Chief Scientific Officer with BioMarck Pharmaceuticals. I am a biochemist and have worked in a variety of areas including protein/peptide chemistry from 1966 to the present. A copy of my Curriculum Vitae was submitted with my previous declaration submitted under 37 C.F. R. § 1.132 on September 6, 2005.

2. I have read and understood the rejections based on the alleged lack of enablement for the full scope of the claims in the Office Action mailed on August 28, 2006 in the above-captioned application. These rejections are based on the Examiner's allegations that the *in vivo* therapeutic treatment of bronchitis, cystic fibrosis, and chronic obstructive pulmonary disease (COPD) comprising the administration of a N-terminal myristoylated peptide comprising at least the first 10 amino acids of MANS is not enabled by the data generated in the "mouse model of asthma." More particularly, the Examiner states that the data provided in my previous declaration were generated using this mouse model but that there was no evidence that data from this mouse model would be predictive of the efficacy of the MANS peptide and fragments for the treatment of the full scope of the diseases encompassed by the claims in the above-captioned application. I respectfully disagree with the Examiner's position and support my position that the murine model that I used to generate my data provided in my previous declaration does provide evidence that this model is predictive of the efficacy of the MANS peptide and of N-terminal myristoylated peptide fragments thereof in the reduction of mucus hypersecretion in a wider scope of diseases in which mucus hypersecretion is a dominant

clinical symptom.

3. My previously submitted declaration stated that my experiments utilized the well-established "ovalbumin-sensitized mouse model of asthma," as disclosed in Eum *et al.* ("Eum"), published in 1995, and submitted with my previous declaration. However, this statement by me was not intended to convey that this model was only useful for studying and evaluating reduction of mucus hypersecretion in asthma, but rather it is useful to study the reduction of mucus hypersecretion in many other diseases and conditions which affect the airway epithelium, such as the diseases and conditions cited in the present set of claims. Eum describes the development of a murine model for antigen-induced bronchial hyperreactivity and airway eosinophilia, which this publication defines as "two hallmarks" of asthma. However, this model is known to be useful to analyze the presence of proteins and other molecules in the bronchoalveolar lavage fluid (BALF). Eum analyzed IL-5 in serum and in BALF of mice, and is useful for studying the presence and levels of any molecules in BALF that may be induced by an antigen challenge, and studied over time or after administration of other molecules. In fact, a later publication by Haile *et. al.* ("Haile"), (1999), attached herewith as Exhibit A, that was authored by many of the same authors as Eum, used the same murine model to study mucus production (see the paragraph bridging pages 896 and 897 and Fig. 8a.) Haile's title refers to the model as the "murine model of asthma" but in the abstract refers to it as the "murine model of allergic pulmonary inflammation."

4. Then in February 2004, Singer *et al.* ("Singer") (previously submitted with Dr. Duncan Roger's declaration as Exhibit 7 of Attachment C), authored by Vargaftig, developer of this mouse model, and the present inventors, was published. Singer reported on the effect of MARCKS-related peptides on mucus hypersecretion and referenced the model in the title as the "mouse model of asthma." However, in the paragraph bridging the 1st and 2nd columns on page 193, the model is referred to as "the ovalbumin (OVA)-sensitized mouse, a well-characterized model of allergic airway inflammation resembling human asthma," with a citation to both the Eum and Haile publications referenced above, as well as earlier publications by Singer (2002) and Vargaftig (2003). This is the same model that I used to test the MANS peptide fragments reported in my previous

declaration.

5. It is my opinion that the phrase "mouse model of asthma" is merely an expeditious historical term used to identify this model because the first publication by Eum studied bronchial hyperreactivity and airway eosinophilia, which are both characteristics of asthma. This model is relevant for studying airway mucus hypersecretion and the effect of the N-terminal myristoylated peptides disclosed in the present invention on airway mucus hypersecretion. Further, the mouse model generates a mucus hypersecretory phenotype on which the peptides are tested. Thus, it is also my opinion that this model is useful for studying other diseases characterized by the symptom of mucus hypersecretion and bronchial hyperreactivity. The first paragraph on page 193 of Singer discloses that "hypersecretion of mucin ...occurs in several respiratory diseases, including asthma, chronic bronchitis and cystic fibrosis." Additionally, the summary paragraph, 1st full paragraph in the 1st column, on page 195, indicates that the results of the studies reported lay the foundations for the development of new compounds for therapy for mucus hypersecretory disorders, such as "asthma, chronic bronchitis and cystic fibrosis." Therefore, it is my opinion that the present murine model is predictive, and thus enabling, for the use of MANS peptide and its fragments, to reduce mucus hypersecretion in diseases in which this symptom is a dominant clinical symptom.

6. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Nov. 20, 2006
Date

Indu Parikh, Ph.D.

44143 v1/DC

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Atty. Docket No: 5051-451IP

In re patent application of
Yuehua LI *et al.*

Group Art Unit: 1633

Serial No. 09/914,020

Examiner: Janet L. Epps-Ford

Filed: December 31, 2001

For: METHODS AND COMPOSITIONS FOR ALTERING MUCUS SECRETION

DECLARATION UNDER 37 C.F.R. §1.132

I, Duncan Fraser Rogers, declare that:

1. I hold the academic position of Reader in Respiratory Pharmacology and administrative position of Director of Postgraduate Studies (Research) at the National Heart & Lung Institute, Imperial College London, UK. I hold a PhD in Physiology (University of London) and am a Fellow of the Institute of Biology (UK). I have worked in the field of respiratory physiology and associated pulmonary diseases for over 25 years (from 1980 to the present). A copy of my Curriculum Vitae was submitted with my previous declaration submitted under 37 is C.F. R. § 1.132 on June 7, 2006.

2. I have read and understood the rejections made in the Official Action in the above-captioned application. mailed on August 28, 2006, based on the alleged lack of enablement by the Examiner. Specifically, the Examiner stated that "while being enabling for inhibiting mucus secretion *in vitro*, and for decreasing mucus hypersecretion *in vivo* via airway administration of the MANS-peptide or active fragments thereof comprising at least the first 10 amino acids of the MANS-peptide in a mouse model of asthma, does not reasonably provide enablement for the *in vivo* therapeutic treatment of bronchitis, cystic fibrosis, chronic obstructive pulmonary disease comprising administration of the compounds of the instant invention."

3. In response to these comments by the Examiner, it is my opinion that the "mouse model of asthma" is a well known model that is useful for studying the effect of treatments on the symptom of mucus hypersecretion in the mouse airways. It is further my opinion that the

association of the "model" to asthma is irrelevant and secondary to the generation of a mucus hypersecretory phenotype in the mouse upon which the effect of a treatment or composition, such as the MANS peptide and fragments thereof disclosed in the above-referenced patent application, can be tested. Thus, one skilled in the pulmonary field would find the "model" to be useful to determine if MANS peptide and fragments thereof inhibit airway mucus hypersecretion that is associated with goblet cell hyperplasia in allergic mice. Administration of compositions to the airways are well known procedures to persons skilled in the treatment of respiratory and pulmonary diseases, such as myself. It is my understanding from a review of the above-referenced application that MANS peptide and its fragments inhibit mucus hypersecretion in airway cells. Mucus hypersecretion is a major clinical symptom of many respiratory diseases, such as asthma, chronic obstructive pulmonary disease and cystic fibrosis. Therefore, it follows that the "mouse model of asthma" would be useful to study the effect of treatments on other diseases and conditions in which mucus hypersecretion is a major clinical symptom that causes deleterious effects.

4. In paragraph 8 of the Official Action, the Examiner questions my reliance on post-filing references to support my position that the present invention is enabled. Firstly, my comments in my previous declaration were prompted, in part, by the Examiner's reliance on my publications, previously referred to as "Rogers (2001 and 2003)," both of which were post-filing; i.e., February 24, 2000 publications. The Li *et al.* ("Li") publication is authored by the inventors of the present application and a comparison of the figures between the present application and the publication shows similar experiments to study the effect of MANS peptide on mucus hypersecretion in NHBE cells. The Li publication represents a peer reviewed publication of the effect of MARCKS via study of the MANS peptide on mucus hypersecretion, and discloses the scientific work by the present inventors which was guided by the disclosure of the above-referenced application.

5. Singer *et al* ("Singer"), also co-authored by the present inventors, is the further extension of the data presented in the Li publication that is discussed and referenced in the first paragraph of this publication. In the second paragraph of Singer, the authors state that they now used the "ovalbumin (OVA)-sensitized mouse, a well-characterized model of allergic airway

inflammation resembling human asthma." This latter statement references four publications, two of which, Eum *et al.* and Haile *et al.*, were published prior to February 24, 2000. Then, Singer goes on to study the effect of MANS peptide in this model on mucus hypersecretion. I consider the progression of experiments from an *in vitro* model in NHBE cells to an *in vivo* model that is well known to persons skilled in the study of respiratory and pulmonary diseases to be a logical step confirming the *in vitro* cell culture results in the complex *in vivo* well-characterized mouse model. As in all experiments, I consider it a logical process to determine the effectiveness of potential therapeutic compounds by evaluating the results in cell culture, then an accepted animal model and eventually into human subjects. In my opinion, the Li and Singer publications were guided by the disclosure of the above-reference application which shows the utility of the MANS peptide and its fragments to inhibit mucus hypersecretion in *in vitro* cell culture. It is well known to utilize accepted animal models to study therapeutic compounds after successful *in vitro* experiments.

6. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

21st Dec 2006
Date

Duncan F. Rogers
Duncan F. Rogers, Ph.D.

45296 v1/DC